From SDS Gels to Supercomputers and More: Highlights of the Symposium Honoring the Scientific Achievements of Dr. Jacob Maizel, Jr.

I still vividly remember the Cray supercomputer (and sitting on the top of it) that our chief, Jacob V. Maizel, Jr., showed to me 15 years ago when I joined the Laboratory of Experimental and Computational Biology (LECB) (formerly the Laboratory of Mathematical Biology)—it was the only one dedicated to biomedical research and was so powerful that, needless to say, I felt excited and proud to be part of the LECB. A few years later, I was reading the *Molecular Biology of the Cell* by Bruce Alberts et al., and what a surprise, Jake was cited as the inventor of SDS gel electrophoresis! (See Second Edition, 1989, page 173, Table 4-9, "Maizel introduced the use of sodium dodecyl sulfate [SDS] for improving polyacrylamide-gel electrophoresis of proteins.") (See also Maizel JV Jr. SDS polyacrylamide gel electrophoresis. *Trends Biochem Sci* 25: 590–2, 2000.)

How are SDS gels related to supercomputers? The answer to this and other questions about the diverse, exciting, and profoundly influential life of Jake Maizel as a scientist was provided by prominent researchers gathered at the symposium, *SDS-PAGE, Genes, and Supercomputers*, organized by Robert Blumenthal to honor Jake's scientific achievements, show our gratitude to him, and somewhat soften our sadness that he is leaving our lab.

In his welcoming remarks to the more than 100 guests, Robert Wiltrout, Director of the CCR, described Jake's long and productive scientific career and emphasized some of his seminal discoveries, including the first observation of the cleavage of large viral precursor molecules to functional proteins. After Jake obtained his PhD in biochemistry in 1959 from Caltech in Pasadena, CA, he briefly joined the NIH as a scientist in the Laboratory of Cell Biology, then became a Professor in the Department of Cell Biology at Albert Einstein College of Medicine in Bronx, NY. In 1974, he returned to the NIH, initially as Head of the Molecular Structure Section of the National Institute of Child Health and Human Development, and from 1984 until his retirement had been Chief of the LECB. His early work was on the identification and characterization of poliovirus and adenovirus structural proteins, mostly by using the SDS gels he invented. In the mid-1970s, he developed an interest in the genes encoding those proteins and also in RNA structure and function (particularly as predicted by computer-assisted analysis) and how RNA can be visualized by electron microscopy. When rapid nucleic acid sequence determination techniques appeared in the late 1970s, he began to apply computers in the analysis of biological sequences. This led to the realization that the biomedical field was ready for the application of supercomputing and to the development of a facility known as the Advanced Biomedical Computing Center to encourage maximum scientific utilization of this technology.

Jacob V. Maizel, Jr., PhD

After the welcoming remarks and introduction of the speakers by Robert Blumenthal, Wolfgang K. (Bill) Joklik emphasized how enormously the invention of SDS gel electrophoresis by Jake has increased the pace of scientific research by giving investigators the ability to separate proteins and determine their size. William Studier reflected on how the SDS gel methodology was critical for understanding *T7* gene expression control. This understanding resulted in the development of the T7-based inducible protein expression system and the recent improvement involving autoinduction of protein expression, where the target protein expression can reach more than half of the total cell protein.

George Vande Woude, who has known Jake for more than 40 years, remembered how he and Jake analyzed the similarity between mouse genomic DNA-containing sequences (sarc) and the acquired cell sequences (src) of Moloney sarcoma virus (*Science* 207: 1222–4, 1980). Others noted additional accomplishments of Jake's, including his seminal discovery of O-linked glycosylation of proteins in the cytoplasm (*Virology* 58: 345–61, 1974), which has had a profound influence on glycobiology.

Bill Joklik said that Jake is one of those few scientists who greatly influenced the work of others, and this became increasingly clear as others spoke.

Charles DeLisi remembered how Jake told him many years ago that there is a way to do whole genomic sequencing, and how this remark affected him later when initiating the human genome project. Matija Peterlin commented that without Jake, he would not have gone into science. Matthew Scharff said that he is most of all indebted to Jake for helping him become a scientist. All of the speakers, who also included William Chin, Ellie Ehrenfeld, Robert Jernigan, Joe Kates, Robert Lenk, David Lipman, Pradman Quasba, and Bruce Shapiro, spoke fondly of Jake—they all, without exception, expressed their love and appreciation for him.

Jake thanked all of the guests for this touching symposium and modestly, as always, concluded that he has only helped other scientists to make discoveries. Although we are all saddened by his departure, we wish Jake much happiness in his new career as a *sea captain!* —Bon voyage!

■ **Dimiter S. Dimitrov, PhD**

■ TRANSLATIONAL RESEARCH

A Novel HIF-1α–Myc Pathway Regulating Hypoxia-induced Cell-cycle Arrest

Koshiji M, Kageyama Y, Pete EA, Horikawa I, Barrett JC, and Huang LE. HIF-1alpha induces cell cycle arrest by functionally counteracting Myc. *EMBO J* 23: 1949–56, 2004.

Solid tumors harbor hypoxic regions that are not only critical for tumor development and progression, but are also associated with resistance to chemotherapy and radiation therapy. Hypoxia-inducible factor 1α (HIF-1α), a basic helix-loop-helix (bHLH) transcription factor of the PAS protein family, plays an essential role in the transcriptional activation of genes involved in angiogenesis and glycolysis, which are required for tumor development and progression. In many human cancers, HIF-1α and HIF-2α, a close member of the HIF-α family, are overexpressed, and their expression levels are correlated with the degree of malignancy. Moreover, genetic studies have shown that *Hif1α*-null tumors grow much slower in a poor vascular environment, as compared with their *Hif1α* wild-type counterparts.

HIF-1α expression is regulated primarily by posttranslational stabilization, resulting from inhibition of the ubiquitin-proteasome pathway that targets the oxygen-dependent degradation domain (ODD) of HIF-1α. HIF prolyl 4-hydroxylases function as oxygen sensors to modify two proline residues within the ODD, thereby enabling the VHL E3 ubiquitin ligase to bind specifically to the hydroxyprolines for HIF-1α polyubiquitination. Accordingly, deletion of the ODD renders HIF-1α stable and capable of binding the hypoxia-responsive element (HRE) and activating the downstream target genes.

Interestingly, apart from stimulation of angiogenesis and glycolysis for cell proliferation and survival, hypoxia also induces cell-cycle arrest, apparently against tumor development. Although the results from *Hif1α*-null cells indicate that HIF-1α is required for hypoxia-induced upregulation of $p21^{cip1}$, a key cyclin-dependent kinase inhibitor that controls the G_1 checkpoint, the role of HIF-1α in the cell cycle remained controversial. Moreover, it remained obscure how HIF-1α transcriptionally activates $p21^{cip1}$ due to the lack of HIF-1α–bound HRE in the promoter.

…we validated that the N-terminal HIF-1α is critical for cell-cycle arrest, indicating a novel mechanism for HIF-1α function.

To provide direct evidence that HIF-1α controls the cell cycle, we took advantage of an ODD-deficient HIF-1α and demonstrated that expression of HIF-1α in normoxia is sufficient to induce G_1 arrest. As expected, HIF-1α activates $p21^{cip1}$ expression, and conversely, HIF-1α–induced cell-cycle arrest is $p21^{cip1}$ dependent. Therefore, HIF-1α induces G_1 arrest via the activation of $p21^{cip1}$.

To understand the mechanism underlying $p21^{cip1}$ activation in hypoxia, we created two functional mutations that inactivate HIF-1α DNA-binding and transcriptional activation, respectively. To our surprise, both mutants were still able to activate $p21^{cip1}$ and to cause G_1 arrest, despite their inability to upregulate known HIF-1α target genes, such as *VEGF*. Thus, neither HIF-1 transcriptional activity nor its DNA binding is required for $p21^{cip1}$ activation, implying a novel HIF-1α function in regulating gene expression.

In pursuit of the distinct function of HIF-1α, we hypothesized that HIF-1α upregulates $p21^{cip1}$ by virtue of functionally counteracting Myc, a known repressor that binds the transcription activator Miz-1 of $p21^{cip1}$. Consistently, hypoxic treatment or HIF-1α expression in normoxia overrode Myc-targeted gene expression; hypoxia/HIF-1α not only upregulated Myc-repressed gene $p21^{cip1}$, but also downregulated Myc-activated genes, such as *TERT* and *BRCA1*. RNA silencing experiments demonstrated